REMARKS

Support for the amendment to claim 5 and the addition of new claim 17 may be found on page 12, where "prolongation of survival" is discussed in the data for the rat heart transplant model, and on page 10, where "treatment" is defined as including prophylactic intervention. Support for new claims 16 and 19 may be found in the first paragraph on page 15.

35 U.S.C. §112 Rejection

Regarding the term "prophylaxis" which is now used in the pending claims, Applicants note that the goal of transplant clinicians in a post-transplant scenario is often prophylaxis and prevention, rather than waiting to provide a transplant drug after rejection symptoms begin to manifest. That is, once symptoms of transplant rejection / graft rejection begin, transplant medications are expected to have a decreased chance of success. As evidence that prophylaxis is the goal of transplantation, numerous transplant drugs are indicated for administration prior to and/or immediately following transplant, times at which rejection has not occurred. For example, the approved label for Neoral® states that the initial dose can be given 4-12 hours prior to transplantation. (Neoral® Package Insert, Revision August 2005, p. 23, submitted herewith as part of an Information Disclosure Statement [IDS]). Applicants also note that "Neoral® is indicated for the *prophylaxis* of organ rejection in kidney, liver, and heart allogeneic transplants." (*Id.* at p. 8). The approved label for Simulect®, another transplant drug, states that it is to be administered once it has been determined that the patient will receive graft and concomitant immunosuppression. (Simulect® Package Insert, Revision September 2005, p. 7, submitted herewith as part of an IDS). Applicants also note that "Simulect® (basiliximab) is indicated for the *prophylaxis* of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids." (*Id.* at p. 4). The approved label for Rapamune®, another transplant drug, states that Rapamue should be administered as soon as possible after transplant. (Rapamune® Package Insert, Revision July 2008, p.4, submitted herewith as part of an IDS). Applicants also note that "Rapamune (sirolimus) is indicated for the *prophylaxis* of organ rejection in patients aged 13 years or older receiving renal transplants." (Id. at p. 3). Thus, not only are transplant drugs often dosed immediately prior to or following a transplant procedure (i.e. times at which there is neither rejection nor symptoms of rejection), but transplant medications are commonly referred to as prophylactic medications. Clearly, one of skill in the art does not require a transplant medication to absolutely 100% guarantee that rejection will not occur in order for a transplant medication to be considered "prophylactic". Any other interpretation of the terms "prophylactic" or even "prevention" is not reasonable in light of the ordinary use of those terms in the field of transplant medication.

The pending application additionally provides data to support the instantly pending claims. In the Graft v. Host experiment on page 12, animals were dosed on four consecutive days – beginning on day 0. On day 0, the test animals typically do not display symptoms of transplant rejection. Moreover, the results showed significant inhibition of lymph node enlargement. Thus, the compounds in the instant application prevented the onset of symptoms of rejection. Accordingly, Applicants have provided experimental support to show that the instantly claimed invention is enabled.

For at least this reason, Applicants respectfully submit that the claims are enabled and respectfully request withdrawal of the 35 U.S.C. §112, enablement rejection of the pending claims.

35 U.S.C. §103 Rejection

The Examiner has rejected currently pending claims 5 and 15 under 35 U.S.C. §103(a) as unpatentable over Heath in view of Albert (both of record), further in views of Goekjian et al. (Expert Opinion Investigative Drugs 2001). The Examiner has previously acknowledged that the PKC inhibitors of Heath are different from those of Albert, but has argued that these compounds are equivalent insofar as they are both PKC inhibitors and are known to be useful for the same purpose.

In response to Applicants' previous argument that Heath teaches that one must choose a PKC inhibitor that targets the PKC isozyme associated with the disorder to be treated, the Examiner now adds Goekjian to the obviousness rejection. The Examiner argues that Goekjian teaches the use of compounds with selective inhibition for beta-1 and beta-2 PKC isozymes for treating graft-versus-host response models in rats. Thus, the Examiner concludes that Heath provides the compounds, Albert provides the disorders, and Goekjian provides beta-1 and beta-2 PKC isozymes for treating graft-versus-host response.

For the reasons of record, Applicants do not concede that Heath suggests the compounds recited in the pending claims (given the genus recited in Heath); nor do Applicants concede the Albert motivates one to select the treatment or prophylaxis of organ or tissue transplant rejection or for the prolongation of graft survival (given the laundry list recited therein). Moreover, from Table 4 of Goekjian, RO32-0432, which the Examiner alleges is selective for PKC beta 1 and 2, is clearly a PKC alpha inhibitor, having an IC_{50} of 9 nM for PKC alpha and an IC_{50} of between 28-31 nM for PKC beta 1 and 2 isozymes.

Heath teaches that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state". The compounds of Heath are PKC beta isozyme specific,[1] and

[1] The two compounds that are subject of the pending claims are shown in Examples 49 and 52 of Heath, wherein these compounds have IC_{50}s for PKC beta-1 and beta-2 isozymes of 0.03 μM. However, the

without some indication that organ or tissue transplant rejection, graft-versus-host disease or prolongation of graft survival would benefit from such PKC beta isozyme specificity, one of skill in the art, upon reading Heath, simply would not select such a compound for treatment or prophylaxis thereof.[2] Albert shows data at [0244] that suggests that the compound of Example 100 is useful for promoting graft survival. However, according to [0228] of Albert, the compound of Example 100 is a PKC alpha inhibitor. Goekjian, like Albert, suggests that a PKC alpha inhibitor may be useful to treat graft-versus-host disease. Thus, upon reading Albert or Goekjian, one of skill in the art would **not** select any PKC beta 1 or 2 inhibitor from Heath for the treatment or prophylaxis of organ or tissue transplant rejection, the prophylaxis of graft-versus-host disease or for the prolongation of graft survival. Moreover, surely neither Albert nor Goekjian would lead one of skill in the art to use the two highly selective PKC beta inhibitors 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione and 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione instead of a PKC alpha inhibitor in such methods.

In sum, as previously argued, Heath teaches a broad genus of selective inhibitors of PKC beta 1 and beta 2, and suggests that selective inhibitors are desirable because only certain PKC isozymes are associated with certain disorders. In Albert's examples, only a PKC alpha inhibitor is shown to be useful in promoting graft survival, and Goekjian provides that a PKC alpha inhibitor may be used to treat graft-versus-host disease. Accordingly, there is no reason that one of skill in the art would select a Heath PKC beta inhibiting compound for the treatment or prophylaxis of organ or tissue transplant rejection, for the prophylaxis of graft-versus-host diseas or for the prolongation of graft survival. There is simply no evidence that the selective PKC beta-inhibiting compounds of Heath are equivalent to the PKC alpha inhibitors of Albert or Goekjian, such that substitution of one for the other would be routine and obvious. For this reason, please withdraw the outstanding obviousness rejection.

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compound of Example 49 has an IC_{50} for PKC alpha of 0.8 μM, which is about 30 times less sensitive than the effect of said compound on PKC beta isozymes, and the compound of Example 52 has an IC_{50} of 0.3 μM, which is 10 times less sensitive than the effect of said compound on PKC beta isozymes. These compounds are clearly specific PKC beta inhibitors.

[2] The Examiner argues that "this does not mean that the artisan [would] avoid using the compounds of Heath to treat transplant rejection or graft-versus-host disease". First, the Office has the burden of showing why an artisan *would* use the compounds of Heath to treat transplant rejection or graft-versus-host disease (not the other way around). Second, Heath teaches very clearly that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state", which indeed would prevent an artisan from using, e.g., a PKC beta inhibitor to treat a PKC alpha disorder.

CONCLUSION

In view of the foregoing distinctions and remarks, Applicants submit that the presently claimed invention is neither disclosed nor suggested by the cited references, and that all the criteria of 35 U.S.C. §112 are satisfied for the instant application. Accordingly, favorable reconsideration of the application is earnestly solicited. Please send any further correspondence relating to this application to the undersigned attorney at the address below.

Respectfully submitted,

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